DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

November 30, 1999

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RE: Petition for Health Claim: Folic Acid, Vitamin B6, and Vitamin B 12 Dietary Supplements and Vascular Disease (Docket Number 99P-3029)

Dear Mr. Emord:

This responds to your health claim petition dated May 25, 1999, submitted to the Food and Drug Administration (FDA) on behalf of Julian Whitaker, M.D., Durk Pearson and Sandy Shaw, American Preventive Medical Association, and Pure Encapsulations, Inc., requesting that the agency authorize a health claim on the relationship between dietary supplements of three B-vitamins, folic acid, vitamin B6, and vitamin B 12, and risk of vascular disease.

FDA has carefully reviewed the scientific evidence submitted in the petition and is not able to conclude that, based on the totality of publicly available scientific evidence, there is significant scientific agreement among experts qualified by training and experience to evaluate such evidence that a relationship between folic acid, vitamin B6, and vitamin B 12 dietary supplements and risk of vascular disease is supported by the available evidence. The agency's conclusion is based on its evaluation of your petition and the information contained therein, conclusions of independent, expert bodies, and its own review of the available observational studies and clinical trials presented in your petition (see section III of this letter).

In your petition you requested that, consistent with the decision in Pearson v. Shalala, 164 F.3d 650 (D.C. Cir. 1999), if the agency found that the proposed claim did not satisfy the standard of significant scientific agreement, the agency authorize the claim with such disclaimer or disclaimers as the agency deemed necessary to avoid a potentially misleading connotation. As explained in the notice that went on display today at the Dockets Management Branch and should be published in the *Federal Register* on December 1, 1999, until a rulemaking to reconsider the general health claims regulations for dietary supplements is complete, FDA intends to deny, without prejudice, any petition for a dietary supplement health claim that does not meet the significant scientific agreement standard in 2 1 CFR § 10 1.14(c). Once that rulemaking is complete, the agency will, on its own initiative, reconsider any petitions denied under this process. The agency will reconsider petitions in the order that it originally received them. Accordingly, the agency is not at this time authorizing the use of the proposed claim with disclaimers.

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At this time, consistent with 2 1 CFR §101.14(c), based on the determination that significant scientific agreement does not exist, the agency is denying without prejudice your petition for a health claim on folic acid, vitamin B6, and vitamin B 12 dietary supplements and risk of vascular disease. Below is the agency's rationale for its conclusions concerning significant scientific agreement.

I. Background: Petition for B-Vitamins and Vascular Disease Health Claim and Preliminary Requirements

Your petition identifies dietary supplements of folic acid, vitamin B6, and vitamin B 12 as the substance that is the subject of the proposed health claim. It also identifies vascular disease as the disease or health-related condition that is the subject of the proposed claim and indicates that vascular disease includes diseases of the heart and circulatory system. Although the petition does not provide an inclusive list of these diseases, it specifically mentions coronary heart disease (p. 5) as the most common and serious form of vascular disease and specifies stroke (p. 6) as another vascular disease that is a leading cause of death in the United States. In addition to coronary heart disease and stroke, studies reviewed in the petition encompass cardiovascular disease, coronary artery disease, myocardial infarction, atherosclerosis, and peripheral vascular disease. The specific claim for which authorization is sought is identified in the proposed model claim as follows: "As part of a well-balanced diet, rich in fruits and vegetables, daily intake of at least 400 µg of folic acid, 3 mg of vitamin B6, and 5 µg of vitamin B12 may reduce the risk of vascular disease."

The petition also provides information with respect to the preliminary requirements for a health claim specified in 2 1 CFR § 10 1.14:

- that the substance conforms to the definition in § 10 1.14 (a)(2);
- that the substance contributes nutritive value and retains that attribute when consumed at levels that are necessary to justify the claim (§ 101.14 (b)(3)(i));
- that use of the substance at the levels necessary to justify the claim is safe and lawful under the applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act (§ 101.14 (b)(3)(ii)); and
- that the substance is associated with a disease for which the general U.S. population is at risk (§ 101.14 (b)(l)).

II. Background: Interpretation of Significant Scientific Agreement

As indicated in 2 1 CFR §101.70(f), the summary of scientific data presented in a health claim petition provides the basis upon which authorizing a health claim can be justified as providing the health benefit. The summary must establish that, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific

procedures and principles), there is significant scientific agreement among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.

You requested that the agency, in its action on your petition, define "significant scientific agreement" in 2 1 CFR § 10 1.14(c) by articulating the principles that guide the agency in reaching its decision. The Working Group on Significant Scientific Agreement of FDA's Food Advisory Committee (1999) recently finalized its report on principles for the agency to use to evaluate scientific validity and interpret significant scientific agreement regarding a substance-disease relationship that is the subject of a proposed health claim. Taking these recommendations into account, the agency intends to issue its guidance about the significant scientific agreement standard by the end of the year. The review and interpretation process to establish significant scientific agreement is described briefly below.

Sound and relevant science in research design and conduct, not the specific type or number of studies, "drives" the decision to authorize health claims. Because available science can be used to support health claim decisions and because these studies are not necessarily designed to address a particular health claim topic, it is not practical to specify the type or number of studies needed to support a health claim. Moreover, each relationship involves a unique set of confounders and measurement issues that must be taken into account in evaluating a specific topic area. Overall, as a minimum, a consistent and relevant body of sound scientific evidence that provides support for the proposed substance-disease relationship must exist before authorization of a health claim can be considered. The types of studies considered in a health claim review should include human studies and frequently also include pre-clinical evidence, e.g., *in vitro* laboratory investigations. Human studies provide the strongest evidence in support of a substance-disease relationship and can be divided into two types: interventional studies and observational studies. In general, interventional studies provide the strongest evidence for an effect of a substance. Various types of observational studies differ because of their designs with respect to their potential contribution to the overall weight of evidence for a proposed relationship, and often do not provide a sufficient basis alone for determining whether a substance-disease association is causally or spuriously related. Mechanistic studies in humans, animal studies, and *in vitro* laboratory studies can provide useful supportive evidence for the validity of a substance-disease relationship, but are often insufficient by themselves to justify a health claim in the absence of more direct evidence obtained from human studies.

The quality and relevance of each individual study is paramount in assessing its contribution to the overall weight of the evidence for the proposed substance-disease relationship. The agency's assessment of the studies presented in support of a proposed claim includes, but is not restricted to, the following considerations in addition to assessment of the inherent strengths and weaknesses of the study design:

- relevance of the population studied
- relevance of the dose and form of the substance studied
- comparisons with appropriate controls (e.g., placebo control group in randomized clinical trials or matched controls in case-control studies)
- appropriate control for confounding variables in design and/or analysis
- appropriate measurement of the substance (intake or status) and the disease outcome. (If disease outcome is not assessed directly, a validated biomarker should be used. Validation implies that the biomarker has an established relationship to the risk of disease and that interventions that alter the biomarker have been established to alter the risk of disease.)

After relevant, good quality studies are identified and their strengths and weaknesses assessed and summarized, a more comprehensive review is based on the body of evidence as a whole. Conclusions regarding the association between nutritional exposures or interventions and outcomes should be supportable by the totality of the evidence. Interpretations should be limited to the research conducted and not require inappropriate extrapolation beyond the available evidence.

Significant scientific agreement refers to the extent of agreement among qualified experts in the field. Significant scientific agreement is not consensus, but rather represents a point in the process of scientific discovery that occurs between the stage of emerging science, where data and information permit an inference, and the final endpoint of consensus within the relevant scientific community that the inference is valid. When determining whether there is significant scientific agreement about a substance-disease relationship, FDA takes into account the viewpoints of qualified experts outside the agency, if such evaluations have been conducted and are publicly available. Information to suggest the existence of significant scientific agreement can be provided based on an objective review that addresses the issues of whether the totality of the evidence consistently and strongly supports the claim through such mechanisms as:

- review publications that critically summarize data and information in the secondary scientific literature;
- documentation of the opinion of an “expert panel” that is specifically convened for this purpose by a credible, independent body;
- the opinion or recommendation of an independent, expert body such as the National Academy of Sciences (NAS), the American Heart Association (AHA), or task forces or other groups assembled by the National Institutes of Health (NIH).

III. Agency’s Review of the Scientific Evidence for the Claim

The summary of scientific data in your petition presents three lines of evidence regarding the proposed claim for a relationship between the three B-vitamins (individually or in combination) and vascular disease risk: evidence regarding the association of levels of circulating homocysteine and vascular disease risk, evidence regarding the association of

the B-vitamins with homocysteine levels, and evidence regarding the association of the B-vitamins and vascular disease outcomes. In addition, your petition cites a number of review articles and related publications as evidence for the existence of significant scientific agreement about the scientific validity of the proposed claim for B-vitamin dietary supplements and vascular disease risk. In the discussion of the agency's review of this information below, the numbers in parentheses are those of the references identified in the bibliography included in your petition as Attachment 1; additional references cited are indicated in the reference list that follows this letter.

A. Association of Homocysteine and Vascular Disease

Most of the evidence presented in your petition addresses the relationship between the three B-vitamins (individually or in combination) and vascular disease risk via relationships with circulating levels of homocysteine, an amino acid formed during the metabolism of the food-derived amino acid methionine. This linkage is based on the presumption that homocysteine level is a validated biomarker for vascular disease risk. As noted above, validation of a biomarker means that the biomarker has an established causal relationship to the risk of disease; that is, that interventions that alter the biomarker have been demonstrated also to alter the risk of disease, as is the case, for example, for the level of circulating low density lipoprotein cholesterol and risk of coronary heart disease. The evidence needed to demonstrate that circulating homocysteine level is a valid biomarker of vascular disease risk must establish that interventions that alter homocysteine levels also affect disease risk. Associations between these two factors can occur for two reasons: a) homocysteine is causally related to vascular disease risk and, thus, a change in homocysteine will change disease risk, or b) homocysteine and vascular disease risk co-vary because of a common relationship to some other factor. In the latter case, interventions to change homocysteine will not have the expected or desired effect on vascular disease risk and could cause a person at risk to delay seeking more effective risk reduction actions. A non-causal correlation between homocysteine and vascular disease risk may be found when the disease condition itself causes a change in homocysteine levels. As another example, consumption of a diet rich in fruits and vegetables might cause the reduction of homocysteine levels because of its high folate content while concomitantly affecting vascular disease risk because such diets also tend to be low in saturated fat, a known risk factor for vascular disease, especially coronary heart disease, risk.

In evaluating the scientific evidence on the use of homocysteine as a biomarker for vascular disease risk, FDA looked for evidence that rules out the second type of association and affirmatively demonstrates that homocysteine levels are causally related to vascular disease risk, that is, that interventions to change homocysteine levels will also change vascular disease risk. Although several lines of evidence suggest that high levels of homocysteine in the blood (plasma or serum) are associated with an increased risk of coronary heart disease, stroke, and peripheral vascular disease, FDA does not agree that homocysteine levels have been validated as a biomarker for risk of vascular disease.

Specifically, as discussed below, FDA does not find evidence that demonstrates that interventions that lower homocysteine levels also lower vascular disease risk.

The earliest evidence suggesting an association between homocysteine levels and vascular disease risk was derived from observational studies of persons with homocystinuria. Homocystinuria is a disease characterized by elevated levels of total circulating homocysteine, usually to three times the population average, although levels as high as 20 times above normal have been reported (51). This disease is caused by a genetically determined impairment of one of several enzymes involved in methionine metabolism and is associated with the development of severe blood vessel (vascular) disease early in life. Whether the high vascular disease risk associated with the homocystinuric condition is caused by the elevated circulating homocysteine levels or whether they are unrelated results of the homocystinuria itself is not known,

Considerable research has been conducted to examine the association of homocysteine levels and risk for atherosclerotic vascular disease and for arterial and venous thromboembolism. Among the retrospective observational studies cited in the petition, Voutilainen et al. (117) found a positive correlation between high homocysteine levels and early atherosclerosis as evidenced by thickened common carotid artery walls in middle-aged men but not women. Other similar studies have reported similar findings (Refs. 52, 100). Higher homocysteine levels have also been associated with an increased number of blocked heart blood vessels in people with no clinical evidence of coronary heart disease or episodes of chest pain without evidence of prior heart attack (Refs. 112, 30). A number of other retrospective studies have reported an association between elevated levels of plasma homocysteine and increased risk of coronary heart disease, stroke, and peripheral vascular disease (14, 33, 115, 88, 17, 44, 78, 50, 98, 36, 116, 75, and 5). Control of other vascular disease risk factors was variable in these studies, adding to the difficulties in interpreting their results. The investigator of one report that examined the possible role of methionine metabolism in coronary artery disease (120) was unable to confirm the initial findings in a later study (12 1). Although these studies are useful in hypothesizing a relationship, they do not provide convincing evidence that homocysteine levels affect vascular disease risk. For example, homocysteine levels have been found to rise in the aftermath of myocardial infarction (Egerton et al., 1996 and Landgren et al., 1995) and stroke (Lindgren et al., 1995); therefore, it is not possible to distinguish whether the observed association of homocysteine with vascular disease reflects a consequence or a cause.

The results from prospective observational studies, which are not subject to the difficulties in assessing temporal associations inherent in retrospective studies, have been less consistent than those from retrospective studies. Ridker et al. (95) found that in post-menopausal women without a prior history of coronary heart disease or stroke, a 24-percent increase in the risk of coronary heart disease and stroke combined was associated with every 5-µmol/L increase in homocysteine level. In a study in Norway, serum homocysteine level was an independent risk factor for coronary heart disease in men and women followed for up to 4 years. Wald et al. (119) found an association between

homocysteine levels and risk of coronary heart disease, and Nygård et al. (79) found a graded relationship between homocysteine levels and risk of death in patients with coronary artery disease. Similar findings were reported in a study on men from an intercountry comparison study involving eleven countries (1). One prospective cohort study showed an association between elevated homocysteine levels and progression of peripheral vascular disease (Taylor et al., 199 1). Another prospective study showed an independent association with stroke (Perry et al., 1995).

By contrast, in the Folsom et al. study (27), although fasting homocysteine level was associated with incidence of coronary heart disease in women (but not in men), this association disappeared when adjustments were made for other coronary heart disease risk factors. A study in Finland of men and women, ages 40 to 64 years, failed to demonstrate an association between serum homocysteine levels and coronary heart disease or stroke (2). A large study of U.S. male physicians (the Physicians' Health Study), ages 40 to 84 years, found a three-fold increased risk of heart attack for men with homocysteine levels above the 95th percentile among controls when followed for 5 years (105). However, when these subjects were followed for 7.5 years, there was no longer a statistically significant association between homocysteine and heart attack or death secondary to coronary heart disease (3) or chest pain secondary to coronary heart disease (Verhoef et al., 1997). An earlier report (not discussed in the petition) from the Physicians' Health Study in which subjects were followed for 5 years did not find a significant association between homocysteine levels and stroke (Verhoef et al., 1994). No increased risk of coronary heart disease was found to be associated with high homocysteine levels in the Multiple Risk Factor Intervention Trial (25).

Studies that show an association of homocysteine with other risk factors for vascular disease highlight the difficulty of assessing its role as an independent risk factor. Associations between homocysteine levels and systolic blood pressure or age have been reported in a number of studies (2, 52, 33, 116, 75, 119, 13, 3, 20, and SO), and some studies have reported a correlation between plasma cholesterol and plasma homocysteine levels (112, 83). Men also tend to have higher homocysteine levels than women (117, 33, 115, and 80), although the gender difference largely disappears with age (17) and may be explained by serum creatinine level, which is higher in men due to greater muscle mass (80).

Overall, these observational data provide suggestive, but not conclusive, evidence for an association of homocysteine levels and vascular disease risk. They do not provide evidence, however, that allows us to determine whether co-varying changes in homocysteine levels and vascular disease risk are caused by homocysteine and, thus, are amenable to interventions designed to affect homocysteine levels or whether these two factors co-vary because of a common relationship to some other factor, perhaps the disease process itself. Without such evidence, it is not possible to predict whether interventions designed to change homocysteine levels will also change vascular disease risk. To date, there are no intervention studies available to provide convincing answers.

The available evidence is, therefore, insufficient to provide validation of homocysteine levels as a biomarker for vascular disease risk.

B. Association of the B-vitamins and Homocysteine

In addition to genetic disorders of enzyme function, high homocysteine levels are associated with environmental factors that include folate, vitamin B6, or vitamin B 12 deficiencies; kidney disease; cancer; and the use of certain drugs (114, 52). That deficiencies of the B-vitamins could influence homocysteine levels is reasonable because they function in the metabolism of methionine and homocysteine: folic acid and vitamin B 12 regulate metabolic pathways catalyzed by the enzymes methylenetetrahydrofolate reductase and methionine synthase, respectively, and vitamin B6 is a cofactor for cystathionine-β-synthase. Treatment with large doses of appropriate B-vitamin cofactors is commonly recommended to reduce hyperhomocysteinemia in patients with genetically caused enzyme disorders and renal insufficiency (Brattström, 1996 and Kang, 1996). Homocysteine levels were considered in the development of the Reference Dietary Intakes as potential indicators of folate, vitamin B12, and vitamin B6 nutritional status, but were rejected as too non-specific for that purpose (Institute of Medicine, 1998).

The evidence presented in your petition regarding the association of folic acid, vitamin B6, and vitamin B 12 and homocysteine comprised twelve observational studies and six intervention studies. Most of the observational studies were case-control studies in which associations of serum levels of the B-vitamins and homocysteine levels were evaluated in patients with a variety of vascular diseases/disorders (coronary artery disease, premature vascular disease, stroke, coronary atherosclerosis) (20, 22, 36, 38, 47, 88, and 103). These studies reported inverse associations (20, 22, 36, 38, 47, 88, and 103) between folic acid and homocysteine levels; inverse associations (20, 88, and 103) between vitamin B 12 and homocysteine levels; and an inverse association (103) between vitamin B6 and homocysteine. Hyperhomocysteinemic men had lower sreum levels of all three B-vitamins than control subjects (113). One study of healthy subjects found that subjects with the lowest folate and vitamin B 12 levels had the highest homocysteine levels, but that there was no association with vitamin B6 levels (48). A cross-sectional study in the Framingham cohort (101) showed that homocysteine levels exhibited a strong inverse association with folate levels, and a weak inverse association with vitamin B 12 and vitamin B6 levels. The only study that assessed dietary intake (109) – also in the Framingham cohort – showed an inverse association between dietary folate and homocysteine levels. In another study that provides supportive evidence for an association of folic acid and homocysteine levels, subjects in the Framingham Offspring cohort assessed after the introduction of folate fortification of grain products had lower homocysteine levels than those assessed prior to fortification (41). Finally, a study of patients with thermolabile methylenetetrahydrofolate reductase (a relatively common, minor genetic defect) suggested that these subjects required higher intakes of folate than controls to regulate homocysteine levels (42).

A few intervention trials were also described in the petition. Two small, metabolic ward studies (39 and 40) showed that restriction of folate intake to the point of marginal deficiency elevated homocysteine levels. One study (8 1) examined the effects of folate intakes of 200, 300, and 400 μg/day (levels reasonably obtained from the diet) and found higher homocysteine levels at the lowest level of folate intake. The remaining intervention studies used levels of supplemental vitamins that greatly exceed the levels specified in the proposed claim in patient populations. Intakes of 1 or 2 mg of folic acid lowered homocysteine levels in patients with coronary heart disease (49), but the effect was attenuated if subjects were already taking multivitamin supplements. In the case-control study described earlier (113), treatment of a small number of the subjects with hyperhomocysteinemia using large doses of the individual vitamins (1 mg folic acid, or 10 mg vitamin B6, or 0.4 mg vitamin B12) normalized homocysteine levels. In a small number of patients with myocardial infarction, the combination of 10 mg folic acid, 150 mg vitamin B6, and 0.4 mg vitamin B 12 reduced homocysteine levels while the levels increased slightly in control patients given a placebo (86).

Overall, there is a sound basis for associations between homocysteine levels and folic acid and – to a lesser extent – vitamins B6 and B 12. However, as discussed previously, these data do not establish an association between the B-vitamins and vascular disease risk, because lowering of homocysteine levels has not been demonstrated to affect vascular disease risk in the general population. Lacking such evidence, homocysteine level cannot be considered a validated biomarker for vascular disease risk and the studies of changes in homocysteine levels with B vitamin intake cannot be inferred as supporting changes in cardiovascular risk.

C. Association of B-Vitamins and Vascular Disease

The evidence presented in the petition for a direct association of the B-vitamins and vascular disease risk is derived mainly from observational studies and a few intervention trials. The available case-control and cross-sectional studies have yielded contradictory results. In one study (5), mean plasma folate and vitamin B 12 levels were found to be lower in elderly persons with coronary artery disease than in controls, although the prevalence of low values did not differ between the two groups. Lower mean folate levels in subjects ‘with coronary artery disease than in controls were also found in younger men (aged 3-50 years) (47, 88); mean vitamin B 12 levels, however, did not differ between the two groups (88). A third case-control study (103) found low vitamin B 12 levels, but not low folate or vitamin B6 levels, to be associated with coronary artery disease risk, while a fourth study (115) reported significantly higher folate levels, but no difference in vitamin B12 and B6 status, in cases with coronary artery disease than in controls. In another study (18), subjects with coronary artery disease had lower pyridoxal phosphate (a vitamin B6 derivative) levels than controls, but folate, vitamin B 12, and total vitamin B6 levels did not differ between cases and controls. In a multi-center study in Europe, subjects with vascular disease were found to have poorer folate and vitamin B6 status than controls, but no difference in vitamin B 12 status (98). In a cross-sectional study of the Framingham cohort (100), plasma concentrations of folate and pyridoxal

phosphate (but not vitamin B 12) and intake of folate (but not vitamins B6 or B 12) were inversely associated with carotid artery stenosis after adjustment for age, sex, and other risk factors. The variability in the findings from these studies does not provide support for a strong or consistent association of the B-vitamins and vascular disease risk.

Results of prospective studies are similarly inconsistent. Three reports utilized data from the National Health and Nutrition Examination Survey I follow-up study to examine the relationship of serum folate status and subsequent disease incidence and mortality. One (28) found a slight but non-significant inverse association with cardiovascular disease mortality. The second (3 1) found an inverse association of serum folate with coronary heart disease in persons younger than 55 years and a positive association with coronary heart disease in persons older than 55 years. The third (32) found a slightly increased risk for stroke associated with low serum folate levels. A followup study of participants in the Nutrition Canada Survey found a significant association between serum folate level and risk of fatal coronary heart disease (76, 77). After adjustment for other risk factors, plasma pyridoxal phosphate, but not folate or vitamin B 12, levels were associated with coronary heart disease incidence among participants in the Atherosclerosis Risk in Communities study (27). A report from the Physicians' Health Study (13) showed no statistically significant association of folate or vitamin B6 levels with myocardial infarction or coronary heart disease mortality. In contrast, a report from the Nurse's Health Study (96) indicated high folate and vitamin B6 intake and high multivitamin use were associated with lower incidence of myocardial infarction and fatal coronary heart disease. These studies have results that are not only inconsistent, but their study designs also do not allow a determination as to whether any observed associations of B-vitamin status or intake with vascular disease reflect a causal relationship.

Available intervention studies do not clarify the potential relationship the B-vitamins and vascular disease risk. One study cited in the petition showed fewer hospital admissions for acute chest pain or myocardial infarction in patients treated by a physician who prescribed supplemental vitamin B6 therapy than among the patients of other local physicians and improved survival in elderly patients with myocardial infarction who had received vitamin B6 (24). The significance that can be accorded this study is limited by the lack of controls and the number of additional variables that were not assessed. In an uncontrolled intervention reported briefly in a letter to the editor (89), regression of carotid artery plaque was noted in patients with elevated homocysteine levels who were treated daily with 2.5 mg folic acid, 25 mg vitamin B6, and 250 µg vitamin B 12 (levels that greatly exceed those suggested in the proposed claim). Another uncontrolled intervention (93) reported beneficial effects on coronary artery calcification among patients with various stages of coronary heart disease following use of a nutritional supplement that provided 45 mg vitamin B6 and 90 µg vitamin B 12 among a large number of other vitamins and minerals. The contributions of these studies to understanding the possible association of the B-vitamins to vascular disease risk is severely compromised by their designs, which included inadequate controls and limitations in the outcomes assessed and populations studied, as well as very high doses of the B-vitamins.

Overall, the limitations in the designs used and conflicting results obtained in the available studies provide an inadequate basis to support a direct effect of the B-vitamins on vascular disease outcomes. These findings strongly suggest that well designed and controlled clinical trials are necessary to establish whether folic acid, vitamin B6, and vitamin B 12 may reduce the risk of vascular disease.

D. Significant Scientific Agreement for the Relationship of the B-Vitamins and Vascular Disease

As noted above, FDA gives consideration to critical reviews by individual experts in its assessment of significant scientific agreement. Your petition cited a number of publications described as literature surveys and meta-analyses as evidence for significant scientific agreement about the relationship between homocysteine and vascular disease risk, the relationship between the B-vitamins and homocysteine, and the inverse relationship between the B-vitamins and vascular disease. Given that circulating homocysteine levels have not been validated as a biomarker for vascular disease risk, the agency concentrated on the publications cited in support of the inverse relationship between the B-vitamins and vascular disease. The agency does not find that these publications provide the level of support for significant scientific agreement regarding the proposed claim that the petition asserts.

The study by Hornberger (37) does not assess the relationship of B-vitamins to vascular disease, but rather presents a cost-benefit analysis of a cardiovascular disease prevention trial using folate supplementation based on certain assumptions about the relationship of folate to cardiovascular disease. The brief editorial by Herzlich (35) on plasma homocysteine, folate, and vitamin B6 concludes that "The question of whether vitamin supplementation can diminish risk of coronary artery disease is an important public health issue which warrants further investigation." Based on an extensive review of folate deficiencies and cardiovascular pathologies, Durand et al. (23) concluded that epidemiological and recent experimental evidence have demonstrated that folate deficiency might increase the risk of cardiovascular disease by increasing circulating homocysteine levels and that the clinical efficacy of folic acid supplementation in reducing cardiovascular disease risk should be evaluated. In their clinical review of the role of folic acid in deficiency states and prevention of disease, Swain and St. Clair (106) conclude that there is some biologic plausibility, but not direct proof, for the assumption that folate supplementation may reduce the risk of heart disease, stroke and peripheral arterial disease.

The meta-analysis of Boushey et al. (9) was an assessment of observational studies designed to determine the risk of elevated total homocysteine levels for arteriosclerotic vascular disease, to estimate the reduction of total homocysteine levels by folic acid, and to calculate the potential reduction of coronary artery disease mortality by increasing folic acid intake. It did not include any studies that directly examined the relationship of folic

acid to vascular disease and, thus, suffered from the same limitations as the original observational studies. Based on their meta-analysis, the authors started by assuming that reducing total homocysteine levels would reduce coronary artery disease mortality. The authors then calculated the effect of increasing folic acid intake under various conditions of intake from diet, supplementation, and fortification, concluding that fortification would be the most effective strategy. The authors concluded that a strong case could be made for the inference that increased folic acid intake (at least 400 μg/day) could reduce arteriosclerotic vascular disease, but that controlled trials would be the most convincing proof. The conclusions of the authors, however, are dependent on the validity of their assumption of a causal relationship between folic acid and vascular disease risk. The authors did not provide data to document the validity of this assumption.

The recent editorial on preventing coronary heart disease by Omenn et al. (87), while supportive of the potential benefits of increasing folic acid intake to at least 400 μg/day, noted that many questions remain regarding the relationship of folate, vitamin B6, and vitamin B 12 to levels of homocysteine, the relationship of homocysteine to cardiovascular disease risk, and the best ways to demonstrate and recommend risk reduction for individual patients and populations. It made no recommendations on intake of vitamin B6 because it concluded that definitive evidence for an inverse association with homocysteine levels and for an optimal dose does not exist, and proposed that the addition of vitamin B 12 to all supplements of folic acid be mandated because of the known potential adverse effect of excess folate in the presence of vitamin B 12 deficiency. The authors, drawing on the experiences of the randomized trials that tested the "seemingly compelling hypothesis that a-carotene would reduce lung cancer and coronary heart disease incidence" but found instead that g-carotene increased lung cancer incidence and cardiovascular disease mortality, also cautioned that "statistical associations do not prove cause-and-effect relationships and do not rule out adverse effects."

The articles cited as evaluating the evidence for a relationship between folic acid, vitamin B6, and vitamin B 12 and reduced risk of vascular disease all emphasized the need for controlled clinical trials to establish the validity of the risk reduction relationship for supplemental vitamins. Even the commissioned review prepared by McCully for incorporation into the petition acknowledges that "no large-scale prospective studies showing prevention of vascular disease by supplemental vitamin therapy have been published, although at least 10 such studies are currently underway." These statements suggest that significant scientific agreement has not been reached.

In assessing significant scientific agreement, the agency gives more weight to reviews conducted under the auspices of credible, independent expert bodies, when they are available, than to reviews by individual investigators. The agency has identified three such reviews that were not referenced in the petition. The first of these, from the National Heart,. Lung, and Blood Institute of the NIH (1995), represents the conclusions of a special panel convened in 1995 to review the scientific evidence about homocysteine's possible link to heart disease. The panel concluded that an elevated

homocysteine level appears to increase the risk of heart disease, stroke, and peripheral vascular disease; however, no studies had been done to demonstrate that lowering the homocysteine level reduces the risk of heart disease. The panel stressed that more research, especially a clinical trial, was needed to understand the possible association between the level of homocysteine and heart and related diseases. The panel also noted that following a well-balanced diet should ensure adequate intake of folic acid, vitamin B6, and vitamin B12 and that there are no data to support the benefit of folic. acid supplements for heart and vessel diseases.

The Institute of Medicine of the NAS (1998), as part of the recent comprehensive review conducted to derive Dietary Reference Intakes for the B-vitamins, examined evidence for the associations of folic acid and vitamin B6 with homocysteine levels and risk of vascular disease. Their authoritative review concluded that the inverse relationship between folate intake and homocysteine concentration is well established, but that there are conflicting data on the association between indicators of folate status or metabolism, homocysteine concentrations, and risk of vascular disease. It also noted that whether increasing the intake of folate could reduce the risk of vascular disease remains to be determined. With respect to vitamin B6, the review found some suggestive evidence for associations with homocysteine and vascular disease risk, but concluded that it is not currently possible to establish a vitamin B6 intake level and/or a homocysteine level for lowest risk of disease.

Finally, the Nutrition Committee of the AHA has prepared a science advisory for healthcare professionals based on a critical review of the data on homocysteine and diet (Malinow et al., 1999). The committee concluded that although there is considerable epidemiological evidence for a relationship between plasma homocysteine and cardiovascular disease, not all prospective studies have supported such a relationship. Moreover, they noted, despite the potential for reducing homocysteine levels with increased intake of folic acid, it is not known whether reduction of plasma homocysteine by diet and/or vitamin therapy will reduce cardiovascular disease risk. Until the results of clinical trials are available, they recommended that emphasis be placed on meeting current dietary recommendations for folate, as well as vitamins B6 and B 12, by intake of vegetables, fruits, legumes, meats, fish, and fortified grains and cereals. For certain high-risk individuals, the committee recommended screening for fasting homocysteine levels and possible treatment with supplements of the three B-vitamins, with appropriate medical evaluation and monitoring, but cautioned that such treatment is still considered experimental pending results from intervention trials.

Thus, the agency finds that, based on the data evaluated and the expert reviews summarized above, there is not significant scientific agreement that the proposed claim for a relationship between folic acid, vitamin B6, and vitamin B 12 dietary supplements and risk of vascular disease is supported by the available evidence.

Sincerely,,

for EA Yetley

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